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# Research on Heterocyclic Compounds, XXXV [1]. Synthesis of 2-Phenylimidazo[1,2-*a*]-pyrazine-3-acetates

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**Summary.** Prompted by the remarkable pharmacological activity shown by the corresponding carboxylic acids and other analogues, a series of 2-phenylimidazo[1,2-*a*]pyrazine-3-acetic acids has been prepared. A multi-step method similar to a synthetic procedure used to obtain Zolpidem, an imidazo[1,2-*a*]pyridine with hypnotic properties has been developed.

**Keywords.** 2-Aminopyrazines; Cyclocondensation reaction; Imidazo[1,2-*a*]pyrazines; *Mannich* reaction.

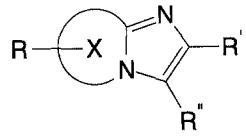
**Untersuchungen an heterocyclischen Verbindungen, 35. Mitt. [1]. Synthese von 2-Phenylimidazo[1,2-*a*]pyrazin-3-acetaten**

**Zusammenfassung.** Angeregt durch die bemerkenswerte pharmakologische Aktivität der entsprechenden Carbonsäuren, wurde eine Reihe von 2-Phenylimidazo[1,2-*a*]pyrazin-3-acetaten synthetisiert. Zu diesem Zweck wurde eine mehrstufige Methode analog zu jener zur Herstellung von Zolpidem, einem Imidazo[1,2-*a*]pyridin mit hypnotischen Eigenschaften, entwickelt.

## Introduction

In the context of our research on heterocyclic anti-inflammatory agents structurally related to the general system **A** (Scheme 1), we have synthesized many new compounds with anti-inflammatory and/or analgesic action [2]. All compounds are characterized by the presence of an acidic function in position 2 or 3 of the imidazole ring ($R'$, $R''$), including carboxylic or acetic groups in the form of esters, amides, or free acids.

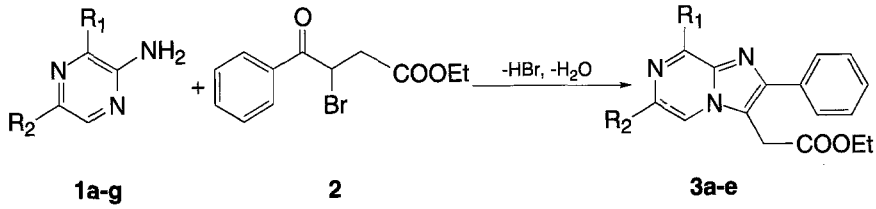
The subject of the present paper is the synthesis of 2-phenylimidazo-[1,2-*a*]pyrazine-3-acetic acids ($X$ = pyrazine ring, $R$ = electron-withdrawing or electron-donating substituents). These derivatives were taken into consideration on the basis of the remarkable pharmacological activity shown by the corresponding carboxylic acids [3] and other analogues during structure-activity relationships studies.



Scheme 1

## Results and Discussion

The required products were first obtained by means of the general synthetic method that we have normally used to prepare imidazo-derivatives of type **A**. This method involves the cyclocondensation of a suitable heterocyclic amine with an α-haloketoester (Method A, Scheme 2).



**1a-g** **2** **3a-e**

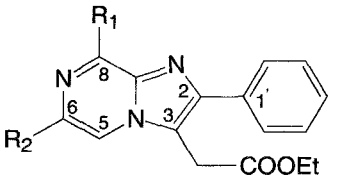
**1a, 3a**: $R_1$ = H, $R_2$ = H
**1b, 3b**: $R_1$ = $OCH_3$, $R_2$ = Br
**1c, 3c**: $R_1$ = $OCH_3$, $R_2$ = H
**1d, 3d**: $R_1$ = $OC_2H_5$, $R_2$ = Br
**1e, 3e**: $R_1$ = $OC_2H_5$, $R_2$ = H
**1f** : $R_1$ = Br, $R_2$ = Br
**1g** : $R_1$ = H, $R_2$ = Br

Scheme 2

The starting 2-aminopyrazine (**1**) was refluxed in anhydrous ethanol or benzene with an equimolar amount of ethyl 3-benzoyl-3-bromopropionate (**2**); the reaction time varied according to the different reactivity of the amines. The structures proposed for the ethyl esters **3a–e** so obtained were confirmed by $^1H$ and $^{13}C$ NMR spectroscopy (Tables 1, 2). However, the yields of these reactions were low, and isolation and purification of the products became difficult. Moreover, the amounts obtained were so small that the preparation of the corresponding acids by hydrolysis was practically impossible. In this context, it must be noted that the acids are the most important compounds for pharmacological studies, and their preparation in suitable amounts is essential. 2-Amino-3,5-dibromopyrazine **1f** and 2-amino-5-bromopyrazine **1g** did not react at all.

Consequently, it was necessary to find a different synthetic pathway which could provide the required compounds in better yields. At last, we have selected a method which is similar to a synthetic procedure used to obtain Zolpidem, an imidazo[1,2-*a*]pyridine with hypnotic properties [4]. This alternative method (Method B, Scheme 3) was tried starting from 2-amino-3-ethoxypyrazine **1e** which in our preceding work on imidazo[1,2-*a*]pyrazine analogues proved to be the most reactive aminopyrazine in cyclocondensation reactions [3].

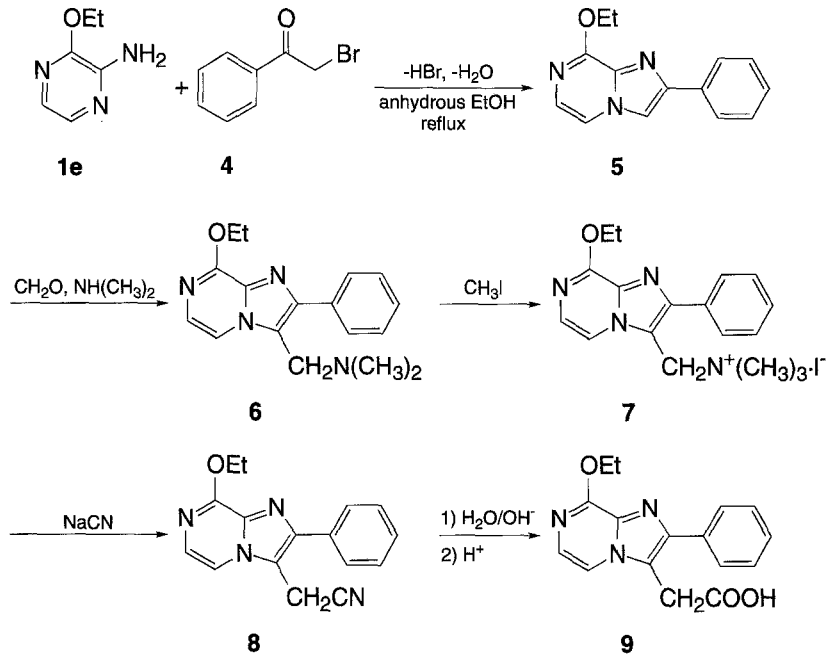
**Table 1.** Ethyl 2-phenylimidazo[1,2-*a*]pyrazine-3-acetates: $^1$H NMR spectra ($\delta$, ppm) in $CDCl_3$




| | H-8 | H-6 | H-5 | H-2′, H-6′ | H-3′, H-5′ | H-4′ | $CH_2COOEt$ | $CH_2CH_3$ | $CH_2CH_3$ | 8-$OCH_3$ | 8-OEt |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **3a** | 9.12(s) | 8.1(d) | 7.97(d) | 7.81(d) | 7.5(m) | 7.45(m) | 4.10(s) | 4.25(q) | 1.30(t) | – | – |
| **3b** | – | – | 7.82(s) | 7.75(d) | 7.43(m) | 7.37(m) | 3.98(s) | 4.21(q) | 1.29(t) | 4.18(s) | – |
| **3c** | – | 7.39(m) | 7.63(d) | 7.78(d) | 7.39(m) | 7.32(m) | 3.95(s) | 4.16(q) | 1.20(t) | 4.10(s) | – |
| **3d** | – | – | 7.88(s) | 7.80(d) | 7.49(m) | 7.41(m) | 4.00(s) | 4.25(q) | 1.31(t) | – | 4.69(q), 1.56(t) |
| **3e** | – | 7.40(m) | 7.63(d) | 7.79(d) | 7.40(m) | 7.33(m) | 3.98(s) | 4.19(q) | 1.24(t) | – | 4.61(q), 1.49(t) |

**Table 2.** Ethyl 2-phenylimidazo[1,2-*a*]pyrazine-3-acetates: $^{13}$C NMR spectra ($\delta$, ppm) in $CDCl_3$

| | C-2 | C-3 | C-5 | C-6 | C-8 | C-8a | C-1′ | C-2′, C-6′ | C-3′, C-5′ | C-4′ | C=O | $CH_2CH_3$ | $CH_2CH_3$ | $CH_2COOEt$ | 8-$OCH_3$ | 8-OEt |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **3a** | 146.5 | 115.0 | 117.0 | 130.0 | 143.0 | 141.0 | 133.0 | 128.6 | 128.3 | 127.9 | 168.0 | 62.0 | 14.0 | 30.5 | – | – |
| **3b** | 145.5 | 116.2 | 112.0 | 119.5 | 153.0 | 132.0 | 133.0 | 128.6 | 128.3 | 127.9 | 168.0 | 62.0 | 14.0 | 31.0 | 55.0 | – |
| **3c** | 145.0 | 116.0 | 112.0 | 126.5 | 155.0 | 132.9 | 133.0 | 128.6 | 128.3 | 127.9 | 169.0 | 62.0 | 14.0 | 31.0 | 54.0 | – |
| **3d** | 146.0 | 116.9 | 112.0 | 120.0 | 153.0 | 132.0 | 133.0 | 128.6 | 128.3 | 127.9 | 169.0 | 62.0 | 14.0 | 31.0 | – | 64.0; 14.5 |
| **3e** | 144.7 | 115.9 | 111.7 | 126.3 | 154.4 | 133.5 | 133.6 | 128.6 | 128.3 | 127.9 | 168.7 | 61.6 | 13.9 | 30.6 | – | 62.7; 14.2 |




**Scheme 3**

In the first step of Method B, **1e** was refluxed in anhydrous ethanol with an equimolar amount of α-bromoacetophenone (**4**) to obtain 8-ethoxy-2-phenyl-imidazo[1,2-*a*]pyrazine (**5**). This product underwent a *Mannich* reaction with formaldehyde and dimethylamine in dioxane/acetic acid solution to afford the 3-dimethylaminomethyl derivative **6**.

The *Mannich* base **6** was then quaternized with methyl iodide to salt **7** which was in turn converted to acetonitrile **8** by reaction with sodium cyanide in methoxy-ethanol/water solution. Finally, the required 2-phenyl-8-ethoxyimidazo[1,2-*a*]-pyrazine-3-acetic acid (**9**) was obtained by hydrolysis with NaOH. The structures of all compounds cited above were confirmed by $^1$H NMR spectroscopic data.

## Experimental

Precoated silica gel Merck 60 $F_{254}$ plates were used for thin layer chromatography; detection of components was performed by UV light and/or treatment with iodine vapor. Chromatographic separations were performed in columns packed with silica gel Carlo Erba (RS, 0.05–0.20 mm). Melting points were determined with a Kofler hot-stage microscope and are uncorrected. Elemental analyses reported in the following text were correct within ±0.4% of the theoretical values. The $^1$H and $^{13}$C NMR measurements were performed on a Bruker AMX-500 spectrometer equipped with a Bruker X-32 computer. Commercially available solvents and chemicals were used for syntheses with the exception of the following compounds that were prepared according to literature methods: 2-amino-5-bromo-3-methoxypyrazine [5], 2-amino-3-methoxypyrazine [5], 2-amino-5-bromo-3-ethoxypyrazine [6], 2-amino-3-ethoxypyrazine [7], 2-amino-3,5-dibromopyrazine [5], 2-amino-5-bromopyrazine [5], and ethyl 3-benzoyl-3-bromopropionate [8].

*Method A, general procedure*

Equimolar amounts of a 2-aminopyrazine (**1**) and ethyl 3-benzoyl-3-bromopropionate (**2**) were dissolved in anhydrous ethanol or benzene and refluxed for 24 h at least. After cooling, the solution was evaporated under reduced pressure to dryness. The residue was treated with saturated aqueous $NaHCO_3$ solution and then extracted 3 times with chloroform. The organic extracts were combined, dried over $Na_2SO_4$, concentrated to a small volume *in vacuo*, and chromatographed on a silica-gel column using the following eluents: chloroform/*n*-hexane (9:1) for **3a**, ether/*n*-hexane (7:3) for **3b**, ether/*n*-hexane (1:1) for **3c**, dichloromethane for **3d**, an ether/*n*-hexane (7:3) for **3e**.

*Ethyl 2-phenylimidazo[1,2-a]pyrazine-3-acetate* (**3a**)

Prepared from 2-aminopyrazine (**1a**); yield: 1.5%; mp.: 87–89 °C (*n*-hexane); $C_{16}H_{15}N_3O_2$ (281.32); calcd.: C 68.31, H 5.37, N 14.93; found: C 68.71, H 5.57, N 15.03.

*Ethyl 6-bromo-8-methoxy-2-phenylimidazo[1,2-a]pyrazine-3-acetate* (**3b**)

Prepared from 2-amino-5-bromo-3-methoxypyrazine (**1b**); yield: 3%; mp.: 113–115 °C (*n*-hexane); $C_{17}H_{16}BrN_3O_3$ (390.24); calcd.: C 52.32, H 4.13, Br 20.47, N 10.76; found: C 51.92, H 4.23, Br 20.42, N 10.39.

*Ethyl 8-methoxy-2-phenylimidazo[1,2-a]pyrazine-3-acetate* (**3c**)

Prepared from 2-amino-3-methoxypyrazine (**1c**); yield: 2%; mp.: 122–124 °C (*n*-hexane); $C_{17}H_{17}N_3O_3$ (311.34); calcd.: C 65.58, H 5.50, N 13.50; found: C 65.20, H 5.70, N 13.80.

*Ethyl 6-bromo-8-ethoxy-2-phenylimidazo[1,2-a]pyrazine-3-acetate* (**3d**)

Prepared from 2-amino-5-bromo-3-ethoxypyrazine (**1d**); yield: 3%; mp.: 89–91 °C (*n*-hexane); $C_{18}H_{18}BrN_3O_3$ (404.27); calcd.: C 53.48, H 4.49, Br 19.77, N 10.39; found: C 53.62, H 4.66, Br 19.40, N 10.59.

*Ethyl 8-ethoxy-2-phenylimidazo[1,2-a]pyrazine-3-acetate* (**3e**)

Prepared from 2-amino-3-ethoxypyrazine (**1e**); yield: 2%; mp.: 98–100 °C (*n*-hexane); $C_{18}H_{19}N_3O_3$ (325.37); calcd.: C 66.44, H 5.88, N 12.91; found: C 66.54, H 5.92, N 12.61.

*Method B*

*8-Ethoxy-2-phenylimidazo[1,2-a]pyrazine* (**5**)

Equimolar amounts of 2-amino-3-ethoxypyrazine (**1e**) and α-bromoacetophenone (**4**) were refluxed in anhydrous ethanol for 6 h. The solid precipitated during the reaction was filtered, washed with ethanol, dried, and treated with 2 *M* aqueous $K_2CO_3$ solution. The aqueous mixture was then extracted with ethyl acetate. The organic extract was added to the ethanolic reaction solution and evaporated under reduced pressure. The reaction product was further purified by extractions with *n*-hexane and then with ether.

Yield: 29%; mp.: 100–102 °C (*n*-hexane); $^1H$ NMR ($CDCl_3$): $\delta = 8.00$ (d, 2 H, H-2′, H-6′), 7.89 (s, 1 H, H-3), 7.70 (d, 1 H, H-5), 7.45 (m, 2 H, H-3′, H-5′), 7.35 (m, 2 H, H-4′, H-6), 4.65 (q, 2 H, $OCH_2CH_3$), 1.60 (t, 3 H, $OCH_2CH_3$) ppm; $C_{14}H_{13}N_3O$ (239.28); calcd.: C 70.27, H 5.47, N 17.56; found: C 70.08, H 5.27, N 17.26.

*3-Dimethylaminomethyl-8-ethoxy-2-phenylimidazo[1,2-a]pyrazine* (**6**)

A solution of **5** (83 mmol) in dioxane was added to a mixture of dimethylamine (40%; 100 mmol), formalin (35%; 100 mmol), and acetic acid (25 ml) in dioxane (85 ml). The reaction mixture was stirred for 1 h at room temperature, followed by 10 h at reflux. The solvent was evaporated, and a solution of $Na_2CO_3$ (10%) was added to the viscous residue which was then extracted with chloroform. The organic extract, concentrated under vacuum, was chromatographed on a silica-gel column (first ethyl acetate/*n*-hexane mixtures, then ethyl acetate) affording a semi-solid product.

Yield: 15.7%; $^1$H NMR ($CDCl_3$): $\delta = 8.00$ (d, 2 H, H-2′, H-6′), 7.70 (d, 1 H, H-5), 7.45 (m, 2 H, H-3′, H-5′), 7.35 (m, 2 H, H-4′, H-6), 4.65 (q, 2 H, $OCH_2CH_3$), 3.90 (s, 2 H, $CH_2N(CH_3)_2$), 2.33 (s, 6 H, $CH_2N(CH_3)_2$), 1.60 (t, 3 H, $OCH_2CH_3$) ppm; $C_{17}H_{20}N_4O$ (296.37); calcd. C 68.89, H 6.80, N 18.90; found: C 68.64, H 7.07, N 18.65.

*3-Dimethylaminomethyl-8-ethoxy-2-phenylimidazo[1,2-a]pyrazine methiodide salt* (**7**)

Methyl iodide (1 ml; 19 mmol) was added to **6** (4 g; 14 mmol) in a mixture of methylene chloride and acetonitrile (14 ml; 3:1). The reaction mixture was left standing overnight and then refluxed for 2 h. After cooling, the precipitated crystals were collected and recrystallized from ethanol.

Yield: 69%; mp.: 140–142 °C; $^1$H NMR (MeOD): $\delta = 8.39$ (d, 1 H, H-5), 7.83 (d, 2 H, H-2′, H-6′), 7.70 (d, 1 H, H-6), 7.65 (m, 2 H, H-3′, H-5′), 7.59 (m, 1 H, H-4′), 5.32 (s, 2 H, $CH_2N^+(CH_3)_3$), 4.70 (q, 2 H, $OCH_2CH_3$), 3.35 (s, 9 H, $CH_2N^+(CH_3)_3$), 1.60 (t, 3 H, $OCH_2CH_3$) ppm; $C_{18}H_{23}IN_4O$ (438.30); calcd.:C 49.32, H 5.29, I 28.95, N 12.78; found: C 49.44, H 5.33, I 29.27, N 13.10.

*3-Cyanomethyl-8-ethoxy-2-phenylimidazo[1,2-a]pyrazine* (**8**)

A solution of **7** (3 g; 6.8 mmol) in methoxyethanol (13.6 ml) was added in portions to a refluxing solution of sodium cyanide (1.6 g; 34 mmol) in methoxyethanol/water (6.8 ml; 1:1). The reaction mixture was refluxed for 5 h and the solvent was removed *in vacuo*. The residue was extracted with methylene chloride and washed with water. The organic layer was concentrated *in vacuo* and recrystallized from *n*-hexane.

Yield: 20%; mp.: 148–150 °C; $^1$H NMR ($CDCl_3$): $\delta = 8.00$ (d, 2 H, H-2′, H-6′), 7.70 (d, 1 H, H-5), 7.45 (m, 2 H, H-3′, H-5′), 7.35 (m, 2 H, H-4′, H-6), 4.65 (q, 2 H, $OCH_2CH_3$), 4.32 (s, 1 H, $CH_2CN$), 1.60 (t, 3 H, $OCH_2CH_3$) ppm; $C_{16}H_{14}N_4O$ (278.32); calcd.: C 69.05, H 5.07, N 20.13; found: C 68.75, H 5.27, N 20.43.

*8-Ethoxy-2-phenylimidazo[1,2-a]pyrazine-3-acetic acid* (**9**)

A solution of sodium hydroxide (80 mg; 2 mmol) in water (3 ml) was added to **8** (0.60 g; 2 mmol) in ethanol (8 ml). The reaction mixture was refluxed for 48 h. The solvent was evaporated, the residue was dissolved by boiling in water, and the solution was filtered while hot. The filtrate was acidified with acetic acid (30%), and the precipitated solid was collected and washed with water and methanol.

Yield: 18.6%; mp.: 162–164 °C (ethanol); $^1$H NMR (MeOD): $\delta = 8.00$ (d, 2 H, H-2′, H-6′), 7.70 (d, 1 H, H-5), 7.45 (m, 2 H, H-3′, H-5′), 7.35 (m, 2 H, H-4′, H-6), 4.65 (q, 2 H, $OCH_2CH_3$), 4.20 (s, 2 H, $CH_2COOH$), 1.60 (t, 3 H, $OCH_2CH_3$) ppm; $C_{16}H_{15}N_3O_3$ (297.32); calcd.: C 64.63, H 5.08, N 14.13; found: C 64.97, H 5.28, N 14.63.

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